# WHAT DO THESE PATIENTS HAVE IN COMMON ?

- 65 y/o male with congestive heart failure ?
- 54 y/o black woman with end stage renal disease ?
- 30 y/o white man with recurrent calcium oxalate stones ?
- 55 y/o white women with end stage liver disease and ascities ?
- 60 y/o black male on lithium therapy with polyuria ?
- 55 y/o white man about to undergo coronary artery bypass surgery ?
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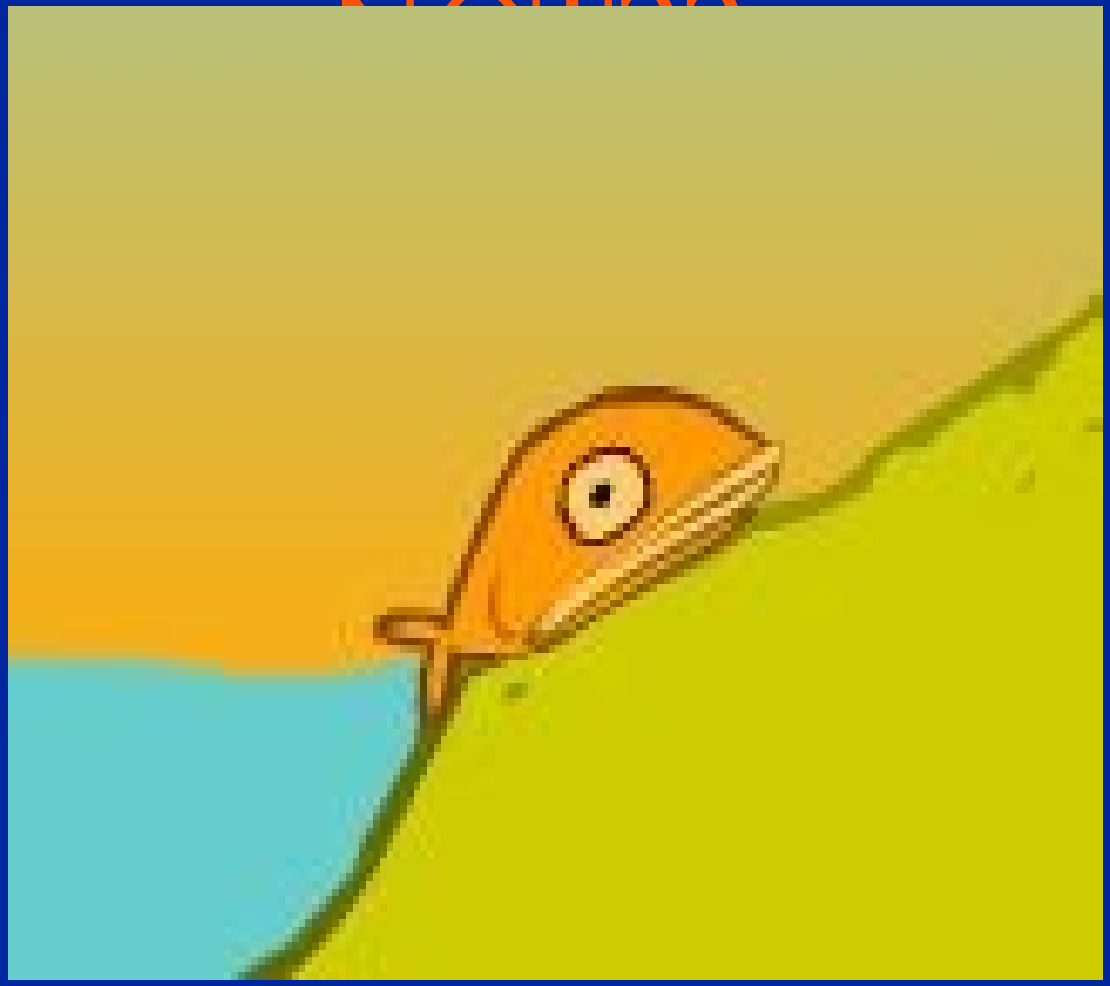
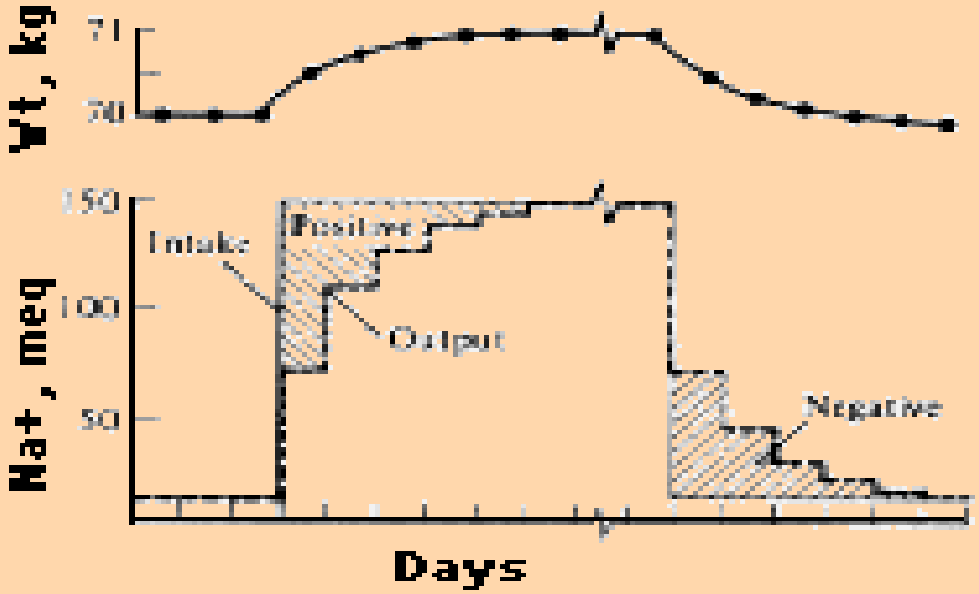
- 50 y/o white women with metastatic breast cancer ?
- 70 y/o man with CHF and severe metabolic alkalosis ?

# WHY

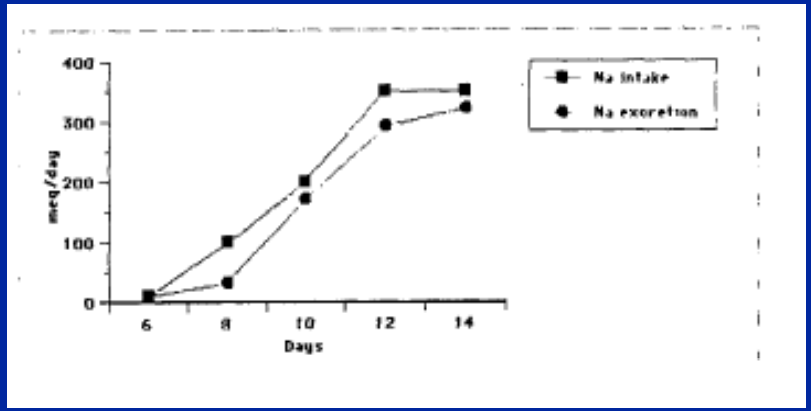


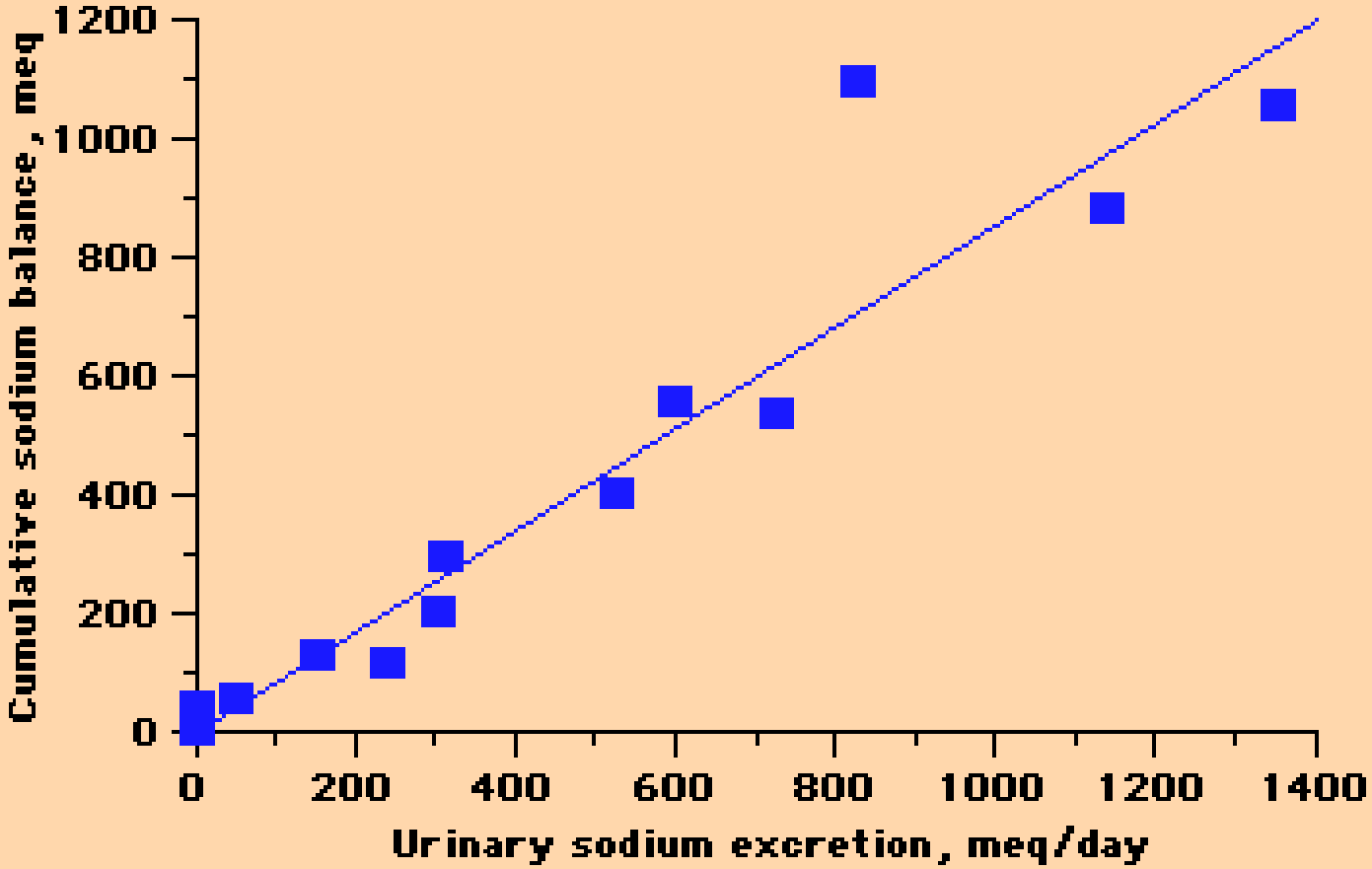



**Response to changes in sodium intake** Effect of abrupt changes in Na+ intake on body weight and renal Na+ excretion in a normal human. The shaded areas refer to changes in total body Na+ stores due to the difference between intake and excretion. See text for details. (From Earley, LE, In: Clinical Disorders of Fluid and Electrolyte Metabolism, Maxwell, MH, Kleeman, CR (Eds), McGraw-Hill, New York, 1972.)

# Sodium Intake and Excretion

- Excretion rises in parallel to intake
- Delay in equilibration
- Area under curve = total sodium retained
- Volume expansion serves as stimulus for higher excretory rate.





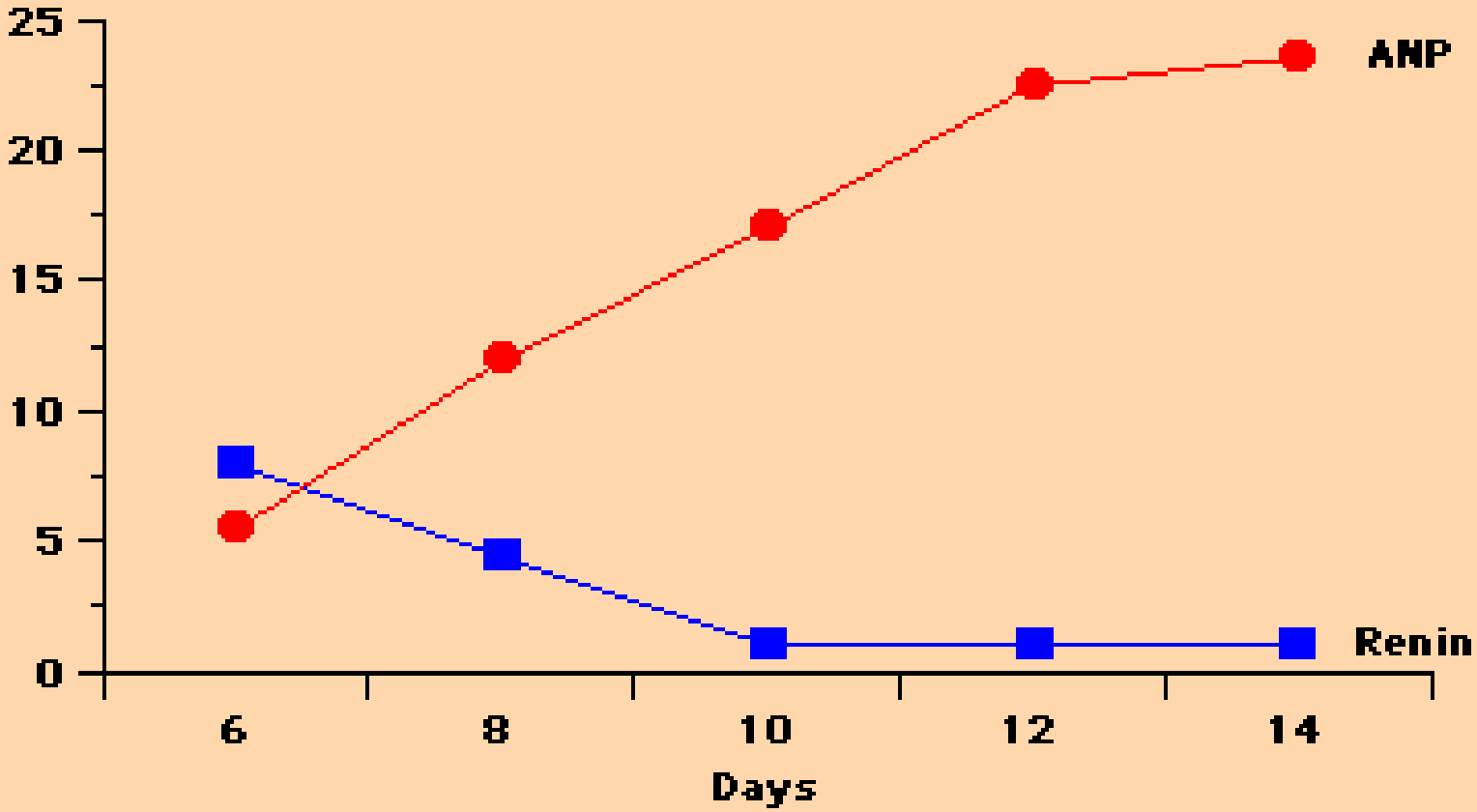

**Positive sodium balance induced by increased sodium intake**

Urinary Na excretion (an indicator of dietary intake in the steady state) as a function of cumulative Na balance in 14 normal subjects studied at different levels of Na intake. As can be seen, net Na balance increases in proportion to the rise in intake, resulting in a progressively greater degree of volume expansion. (Data from Walser, M, Kidney Int 1985; 27:837.)

# VOLUME REGULATION

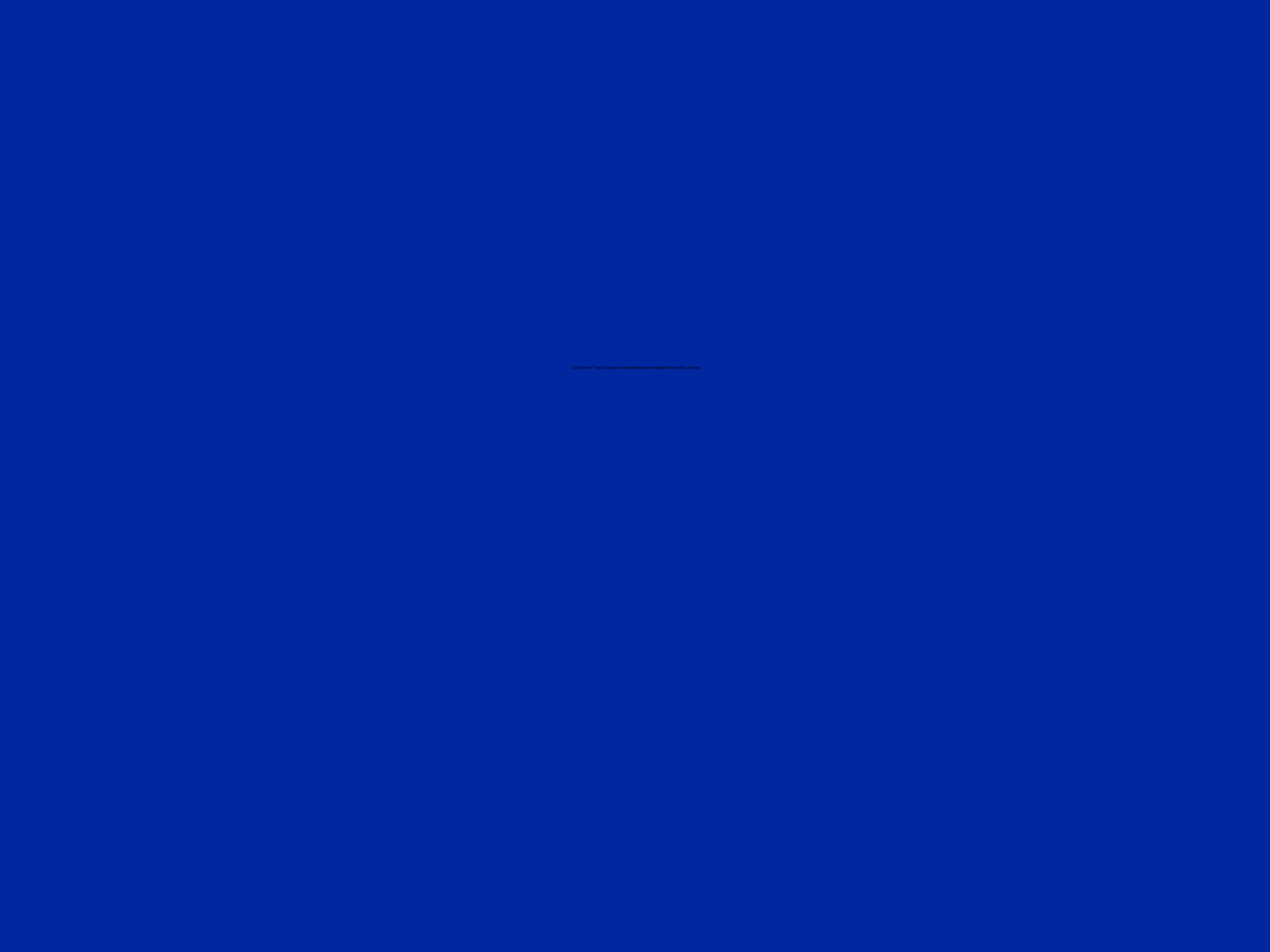
* **Neurohumoral Response**
  - **Renin-Angiotensin-Aldosterone**
  - **Arginine Vasopressin**
  - **Sympathetic nervous system - NE**

* **Renal Response**
  - **Sodium & Water Excretion**
  - **Alteration in the delivery of $H_2O$ and $Na^+$ to distal tubular sites is the major determining factor.**




**Hormonal response to increasing sodium intake** Increasing plasma levels of atrial natriuretic peptide (ANP) and falling plasma renin activity in normal subjects given a progressively increasing sodium intake from 10 to 350 meq/day after a 5-day equilibration period. These hormonal responses promote urinary excretion of the excess sodium. (Data from Sagnella, GA, Markandu, ND, Buckley, MG, et al, Am J Physiol 1989; 256:R1171.)


QuickTime™ and aGraphics decompressorare needed to see this picture.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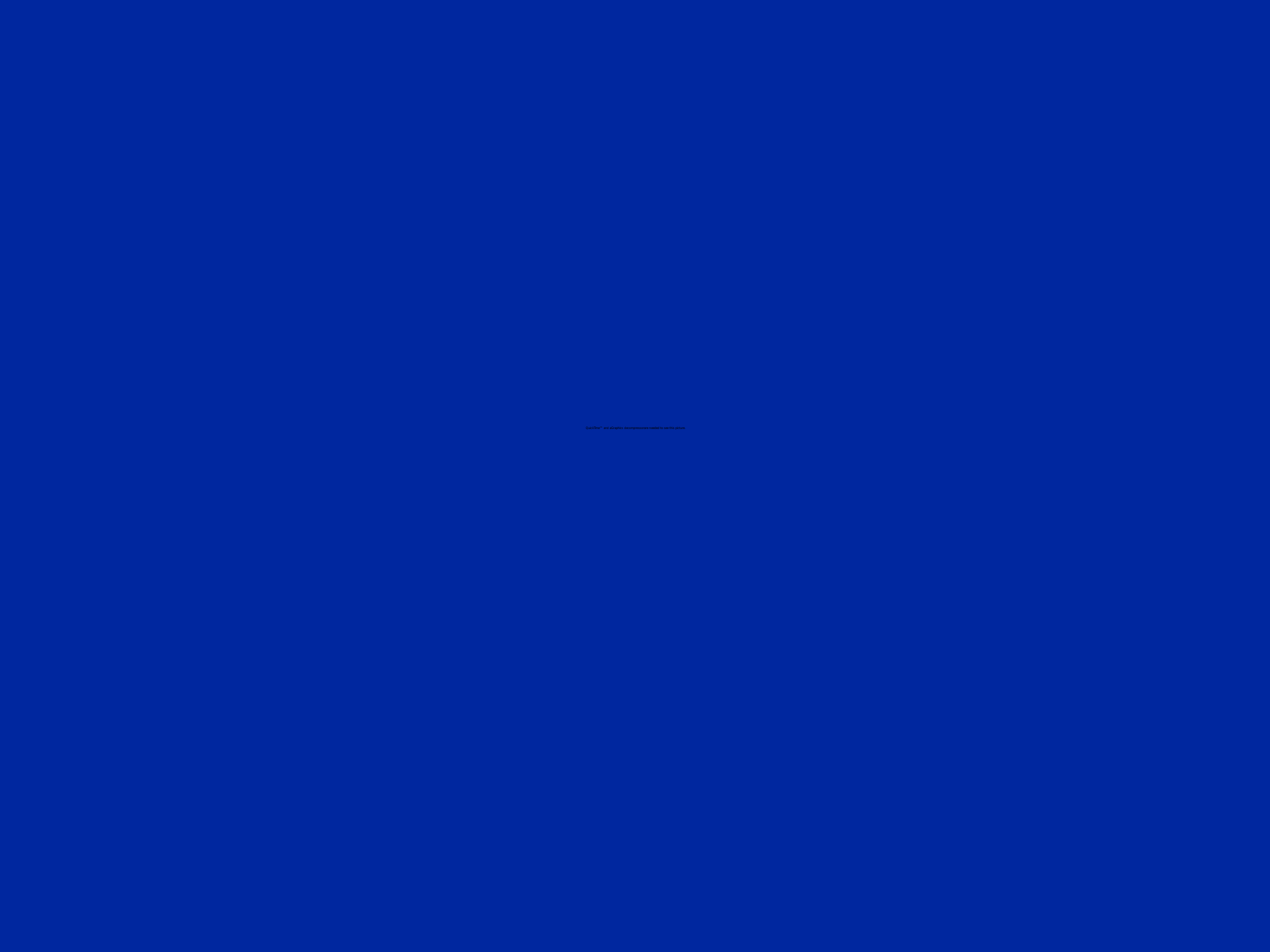
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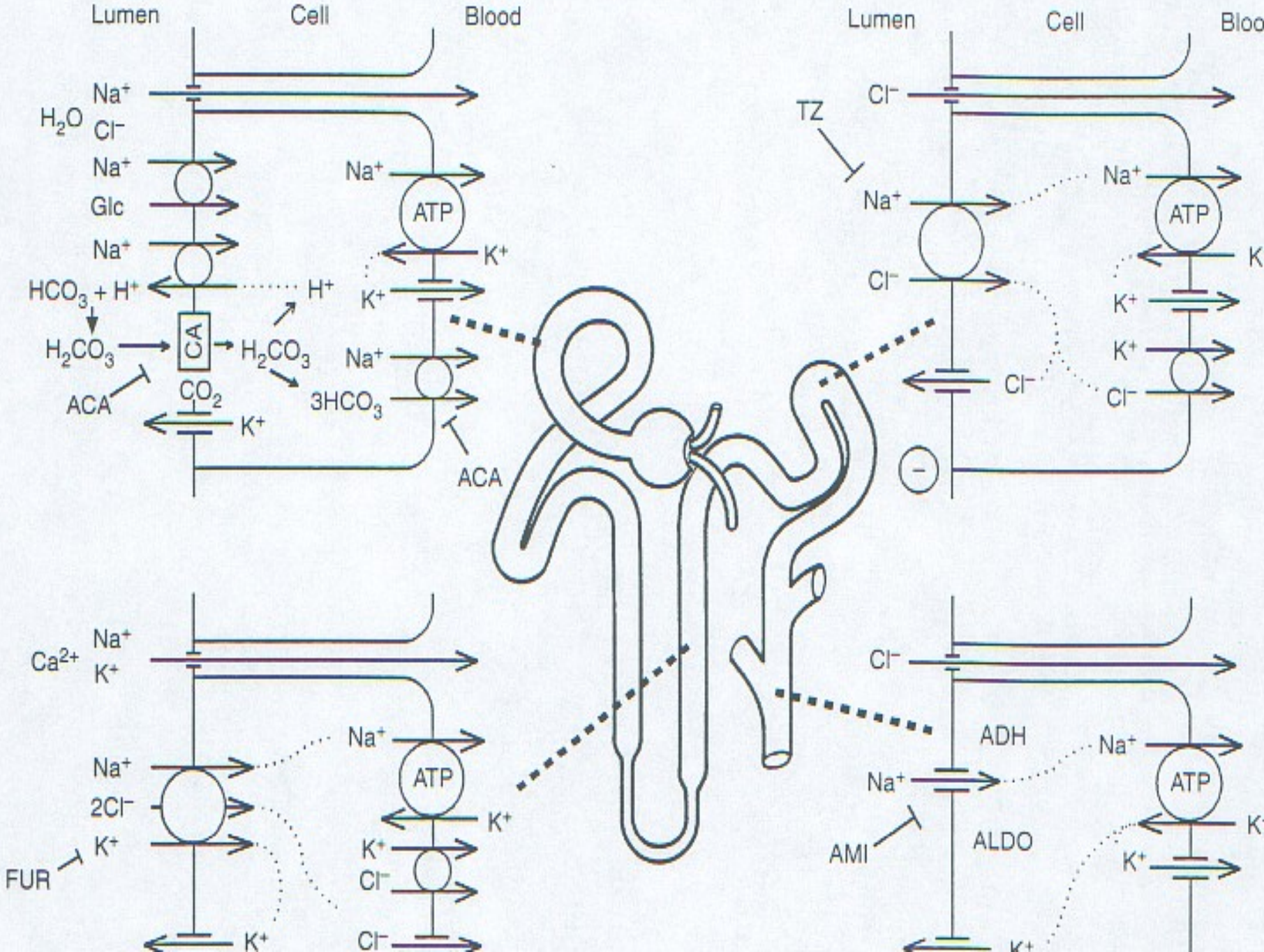
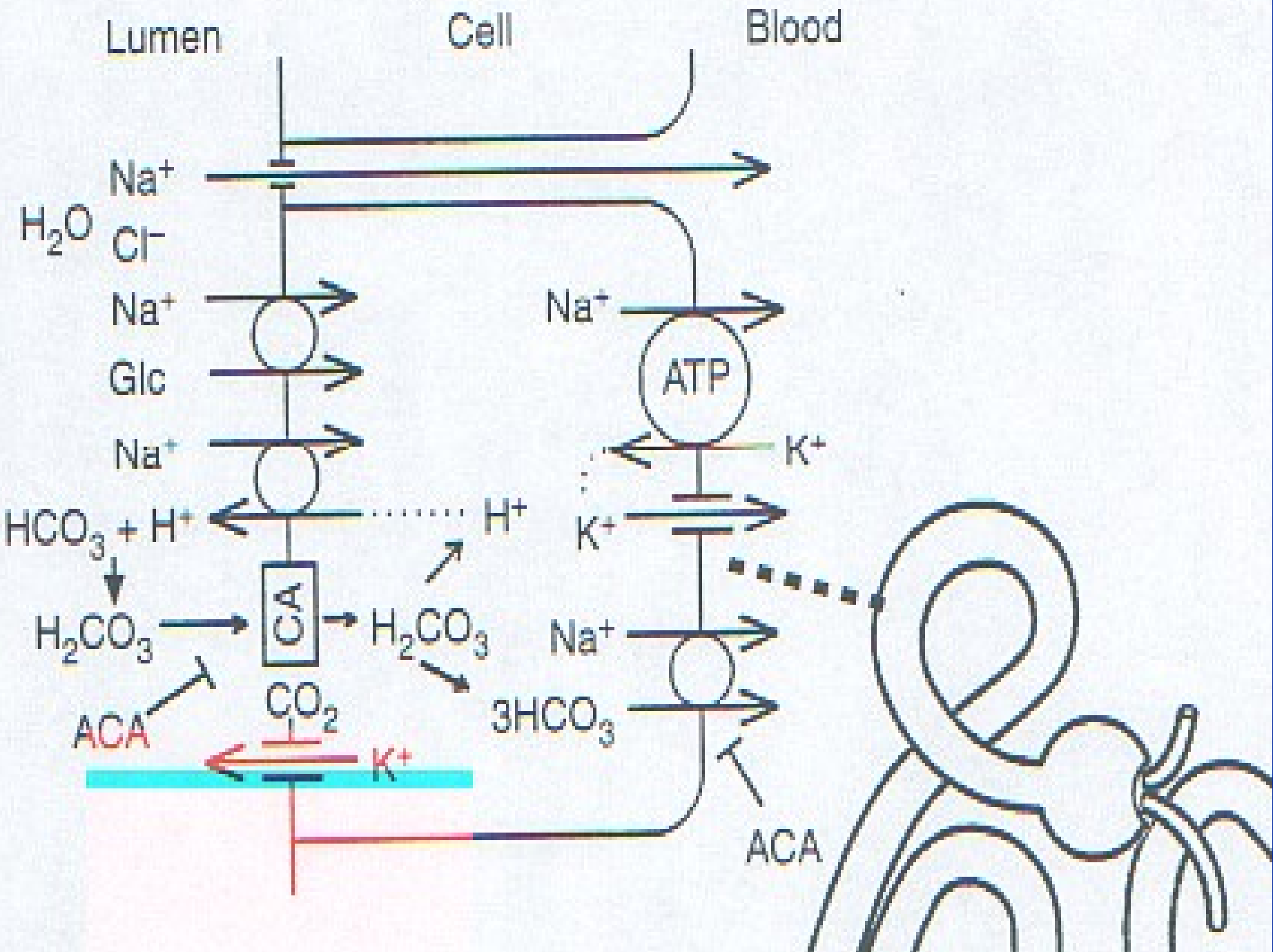

Lumen
Cell
Blood
Na+
H2O
Cl−
Na+
Glc
Na+
HCO3 + H+
H+
H2CO3
CA
H2CO3
ACA
CO2
K+
Na+
3HCO3
K+
ATP
K+
ACA
Lumen
Cell
Blood
Cl−
TZ
Na+
Cl−
Na+
ATP
K+
K+
K+
Cl−
Cl−
Ca2+
Na+
K+
Na+
2Cl−
K+
FUR
K+
Na+
ATP
K+
K+
Cl−
Cl−
Cl−
ADH
Na+
AMI
ALDO
Na+
ATP
K+
K+

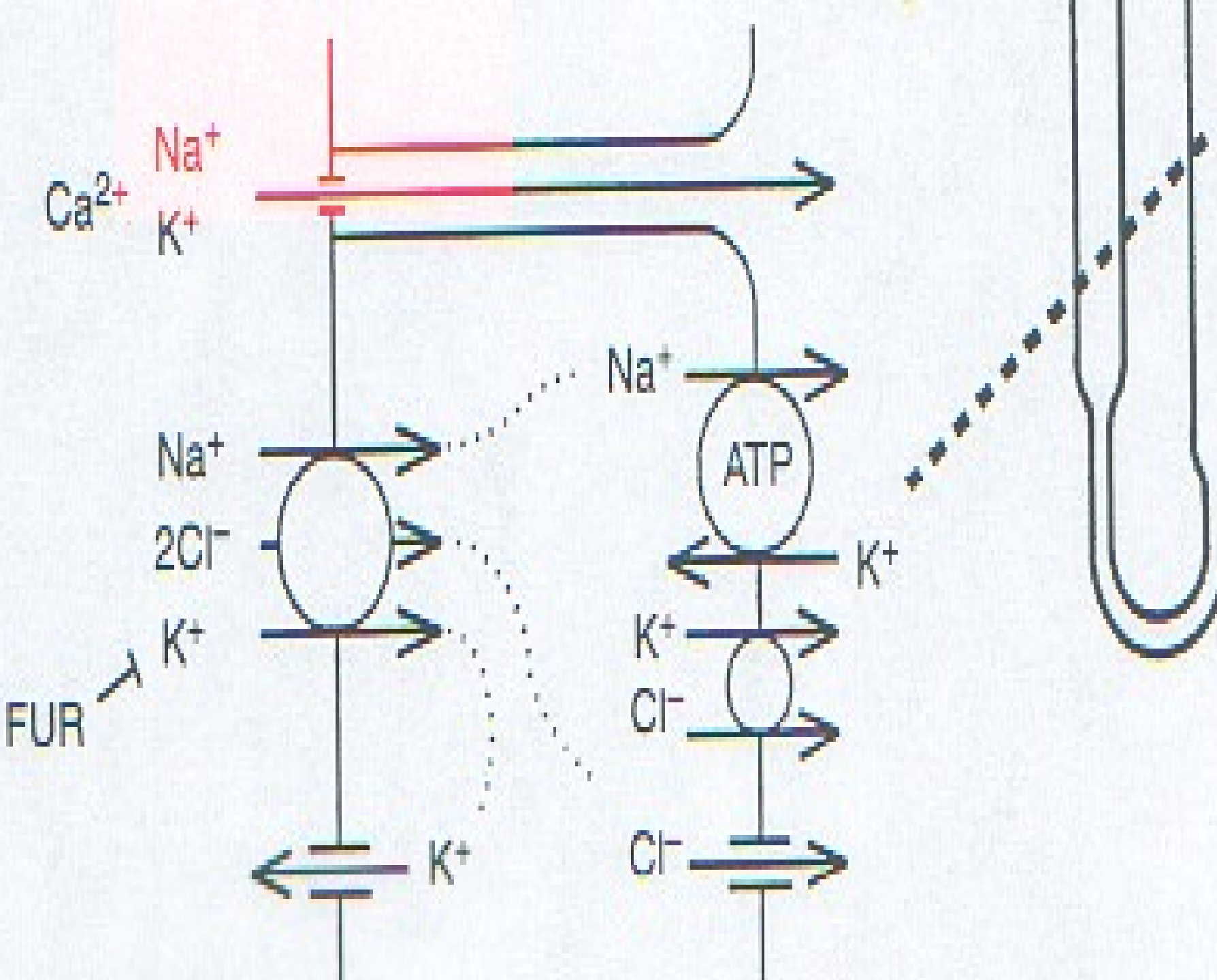
# ANATOMICAL-FUNCTION CORRELATIONS

- **Proximal tubule**
  - **Reabsorbs 65-70% of the filtered NaCl & $H_2O$**
  - **Reabsorbs 90% of filtered $HCO_3^-$ ($H^+$ secretion)**
  - **almost all filtered glucose and amino acids**
  - **$K^+$, phosphate, calcium, magnesium, urea, uric acid**
  - **Secretes organic acids (e.g. urate) and bases, including many protein bound drugs**
  - **Major site of nephron ammonia production**


Lumen
Cell
Blood
Na+
H2O
Cl−
Na+
Glc
Na+
HCO3 + H+
H2CO3
CA
H2CO3
H+
CO2
ACA
K+
Na+
ATP
K+
K+
Na+
3HCO3
ACA

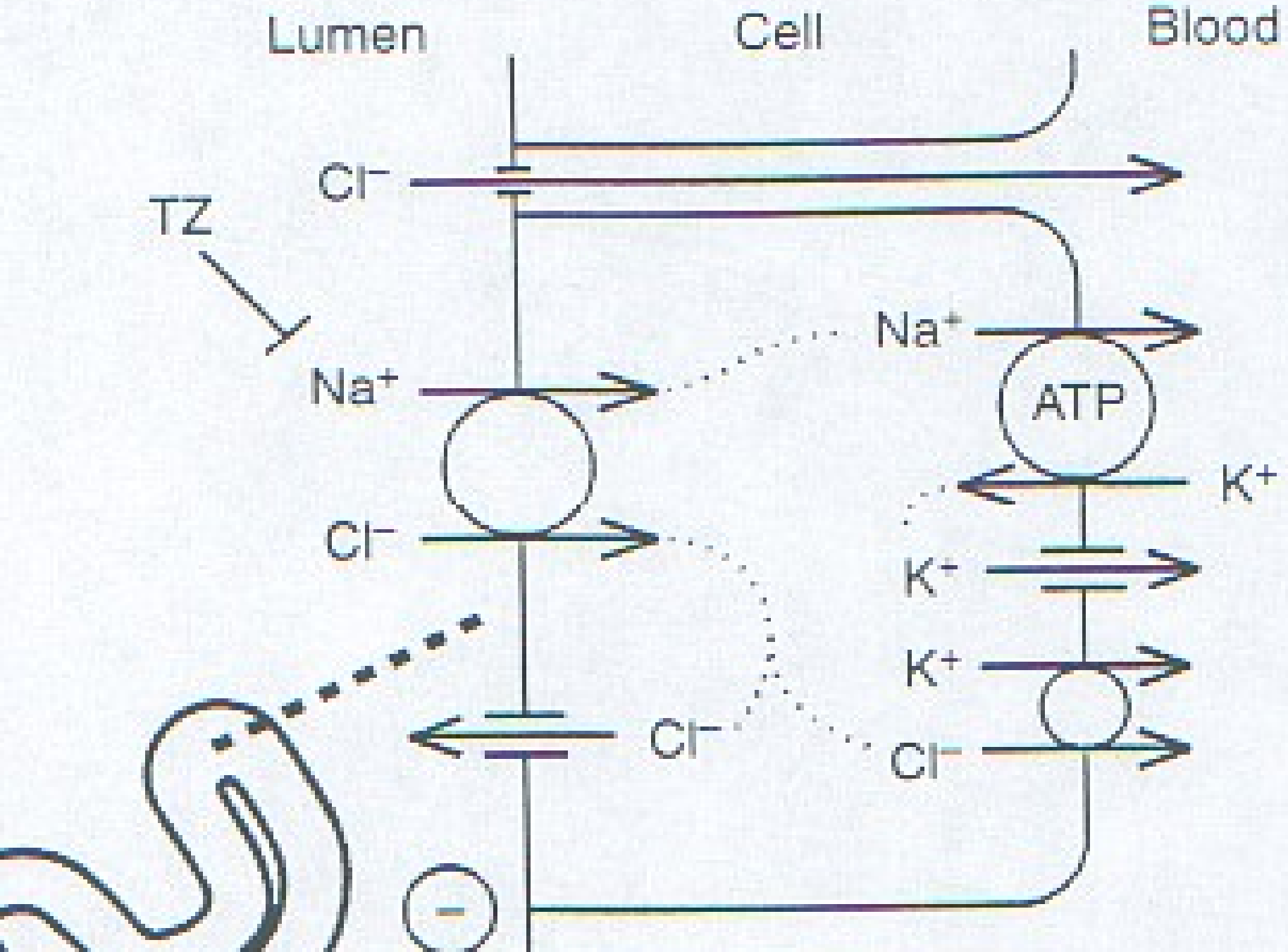
# ANATOMICAL-FUNCTION CORRELATIONS

- **Loop of Henle**
  - **Reabsorbs 35-40% of filtered NaCl**
  - **Countercurrent multiplier (active NaCl transport) “ diluting segment”**
  - **Site of calcium & magnesium reabsorption**
  - **Site of “high ceiling” diuretic action**


Na+
Ca2+
K+
Na+
ATP
Na+
2Cl−
K+
K+
FUR
K+
Cl−
K+
Cl−

# ANATOMICAL-FUNCTION CORRELATIONS

- **Distal tubule**
  - **Reabsorbs 5-8% NaCl**
  - **$Na^+$ & $Cl^-$ cotransporter (electroneutral)**
  - **Major site of $Ca^+$ excretion (dissociated from sodium) [early cortical distal nephron, TAL, & connecting segment]**
  - **$Ca^+$ reabsorption transcellular. HCTZ enhances $Ca^+$ reabsorption - ? Mechanism.**
  - **KCl cotransport on basolateral side**

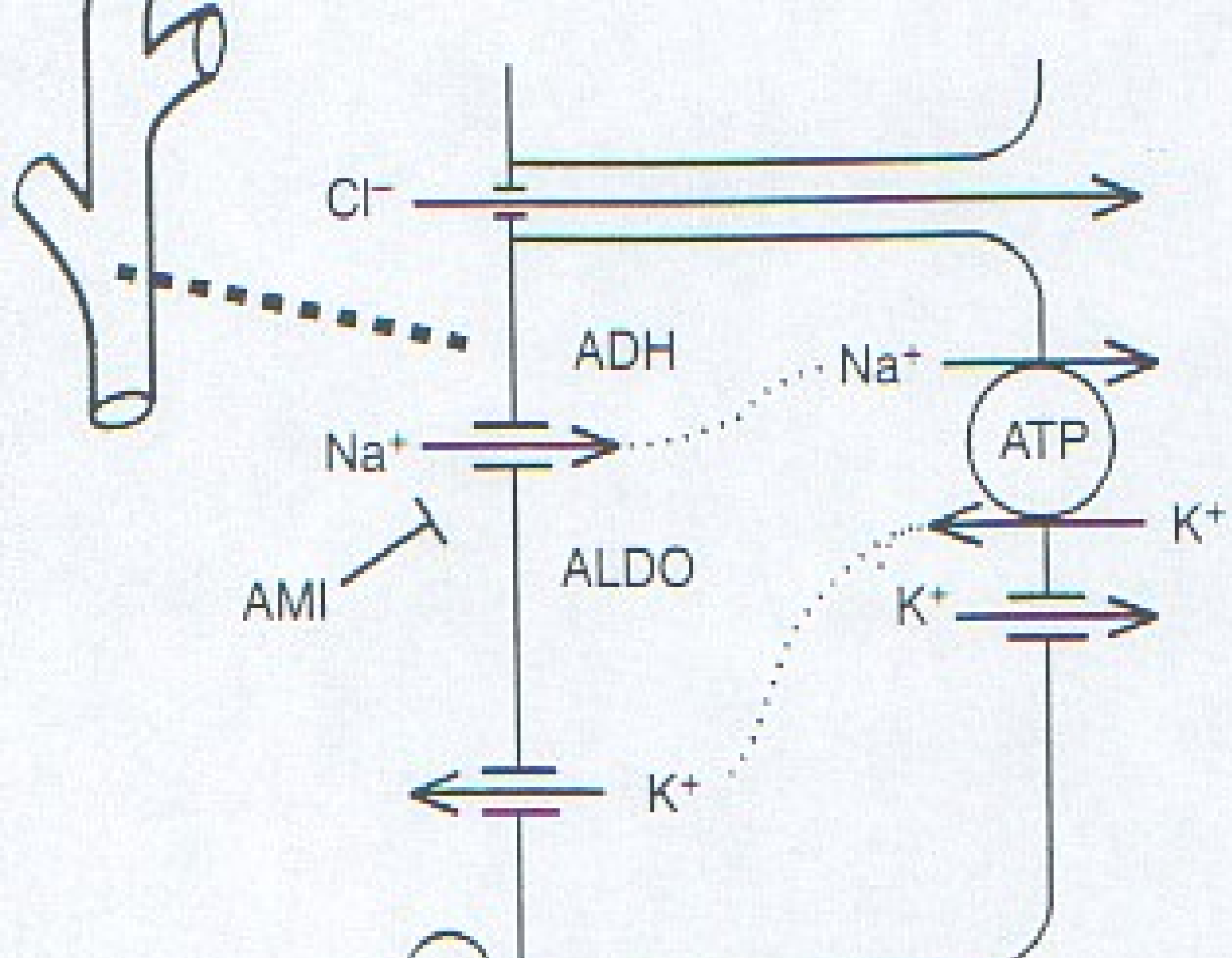

Lumen
Cell
Blood
Cl⁻
TZ
Na⁺
Na⁺
ATP
K⁺
Cl⁻
K⁺
K⁺
Cl⁻
Cl⁻
−

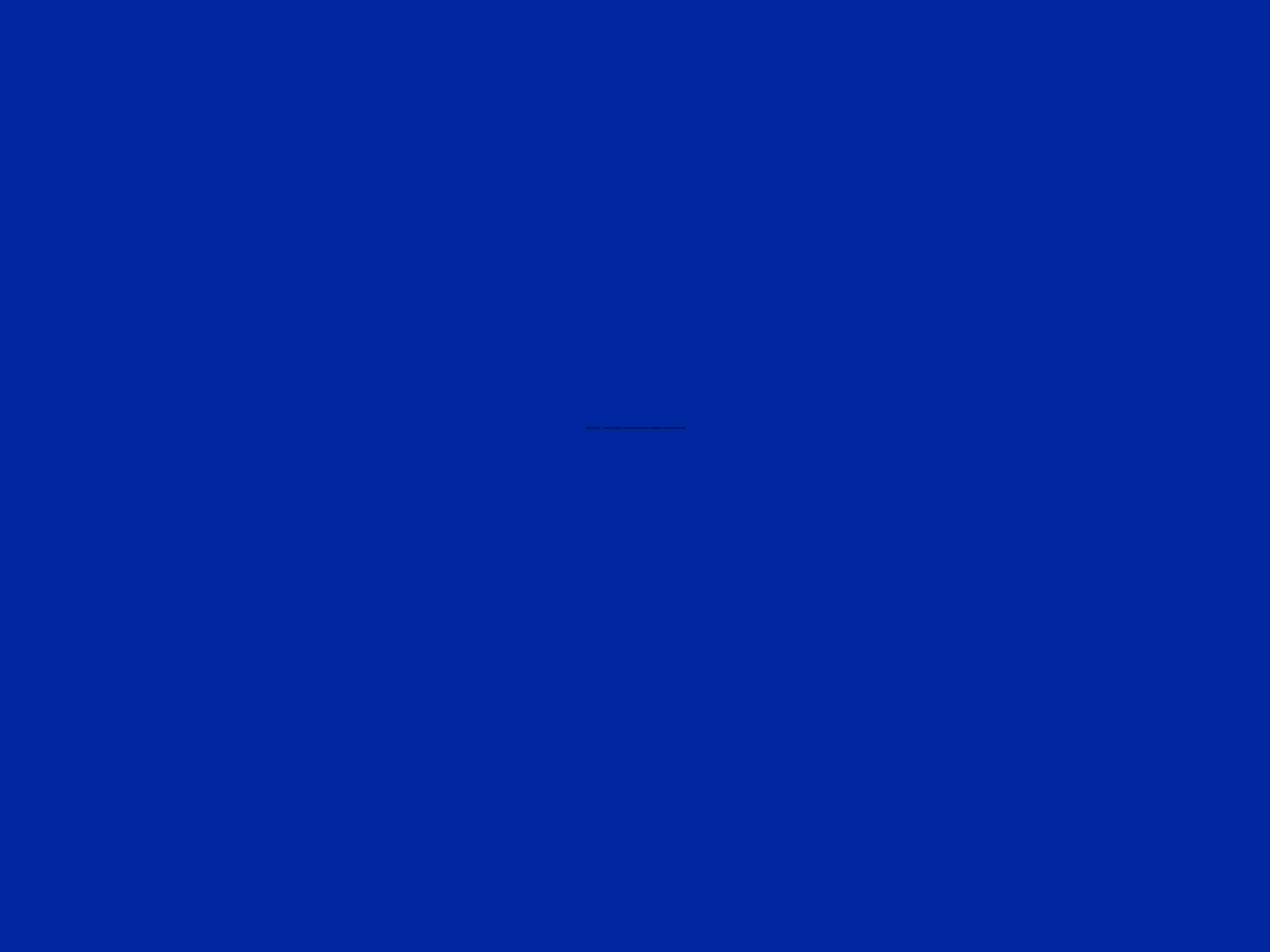
# ANATOMICAL-FUNCTION CORRELATIONS

- **Connecting segment & Cortical collecting tubule**
  - **Principal cells absorb $Na^+$and $Cl^-$ & secrete $K^+$(partial aldosterone influence)**
  - **Intercalated cells secrete $H^+$, reabsorb $K^+$, and in metabolic alkalosis - secrete $HCO_3^-$**
  - **Reabsorb water in presence of antidiuretic hormone**

# ANATOMICAL-FUNCTION CORRELATIONS

- **Medullary collecting tubule**
  - **Site of final modification of urine**
  - **Reabsorbs NaCl; urine [NaCl] can be reduce to < 1 meq/l**
  - **Reabsorbs water and urea relative to amount of antidiuretic hormone present. (dilute or concentrated urine)**
  - **Secretes $H^+$ and $NH^3$; urine pH can be reduced to 4.5 - 5**
  - **Capable of secretion or reabsorption of $K^+$**


Cl⁻
ADH
Na⁺
Na⁺
ATP
K⁺
AMI
ALDO
K⁺
K⁺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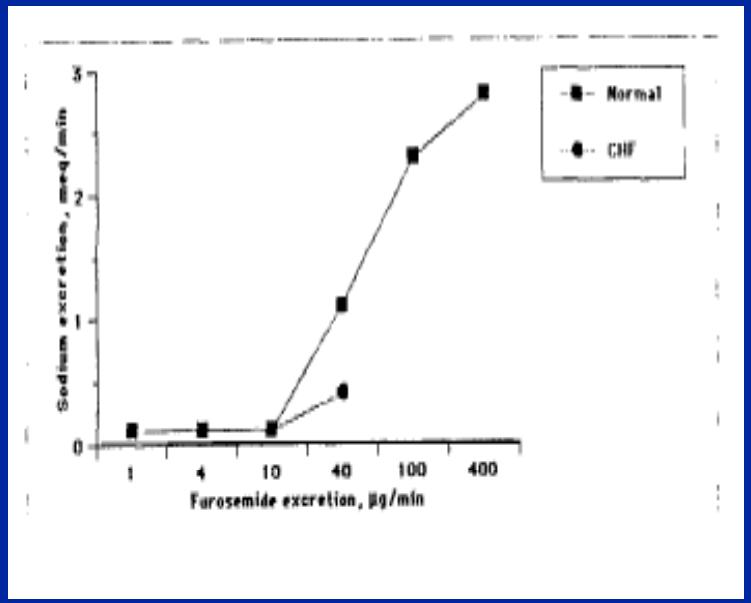
# Diuretics
## Kidney Selectivity

- GFR &  Proximal tubular secretion & water reabsorption
- Luminal activity (except spironolactone)
- Tubular concentration = 20 - 100 fold higher than plasma
- Consequences
  - Larger doses associated with side effects in other organ systems
  - Diuretics compete with other substances for proximal tubule transport proteins. Competition may lead to decreased secretion
  - Decrease in GFR = decrease in diuretic delivery

# DIURETICS
## Dose Response: Sodium Excretion

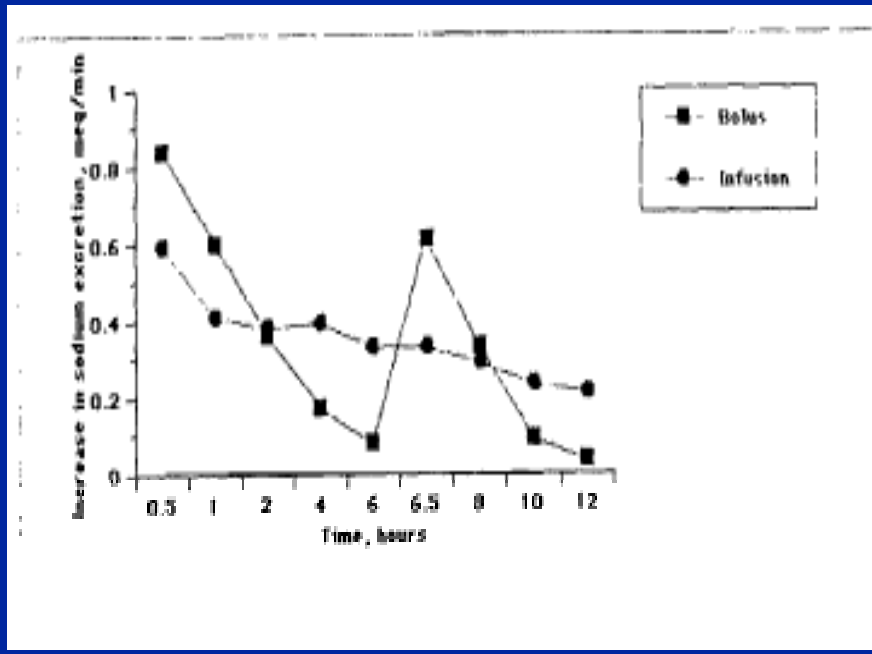
- **Pharmacodynamics**
  **"effective dose"**
  **"maximal dose"**
  **Diuresis is threshold dose dependent.**

- **Any condition that increases sodium reabsorption in nephron segments not acted upon by a specific agent has the potential to decrease the overall responsiveness to a diuretic.**



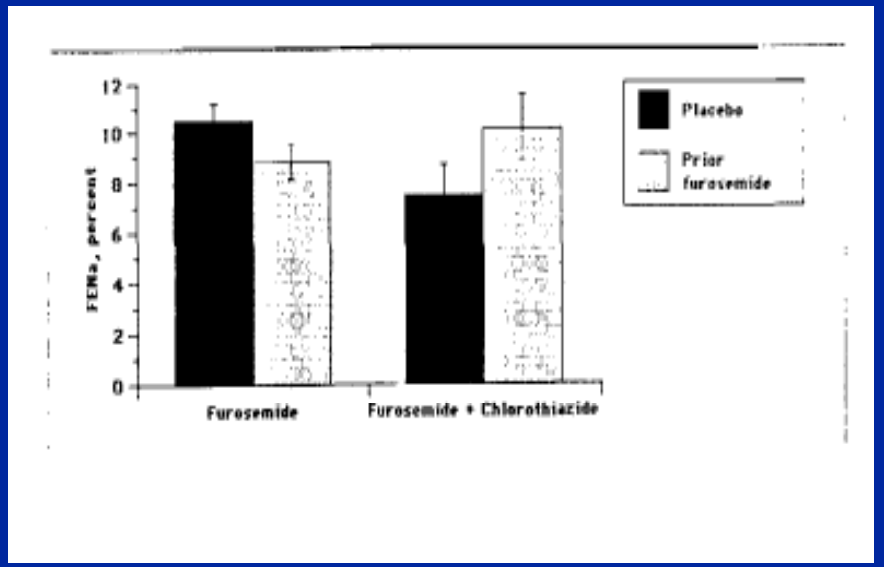
# DIURETICS
## Routes of Administration vs. Response

- Peak diuresis occurs at first dose of loop agent
- Bolus administration gives greater initial but shorter total response than infusion.
- Peak natriuretic response to 2ond bolus is 25% < first.
- Infusion therapy provides 30% greater increase in total Na excretion than bolus. Better rate of diuretic excretion.
- Natriuretic response declines over time.



# DIURETICS
## Loop Diuretic: Effect on Distal Sodium Transport

- Furosemide causes a lesser increase in FENa in subjects previously treated with this diuretic.
- The increase in FENa is significantly greater with the combination of a thiazide + furosemide in subjects previously treated with furosemide.
- Loop diuretics induce an increase in distal sodium reabsorption.



# Limited efficacy of diuretics in chronic renal failure

| Pharmacokinetics | Normal | Failure |
|---|---|---|
| GFR *ml/min* | 100 | 10 |
| Filtered Na mEq/min | 15 | 1.5 |
| Thiazide (10% inhibiton) *mEq/min* | 1. 5 | 0.15 |
| Furosemide (25% inhibition) *mEq/min* | 3.75 | 0.375 |
| Combination (35% inhibition) *mEq/min* | 5.25 | 0.525 |

Combinations of the two types of diuretics have been found enormously successful in renal failure patients who had been resistant to either class of diuretic alone.

## PHARMACOKINETICS

Maximizing the diuretic response in chronic renal failure

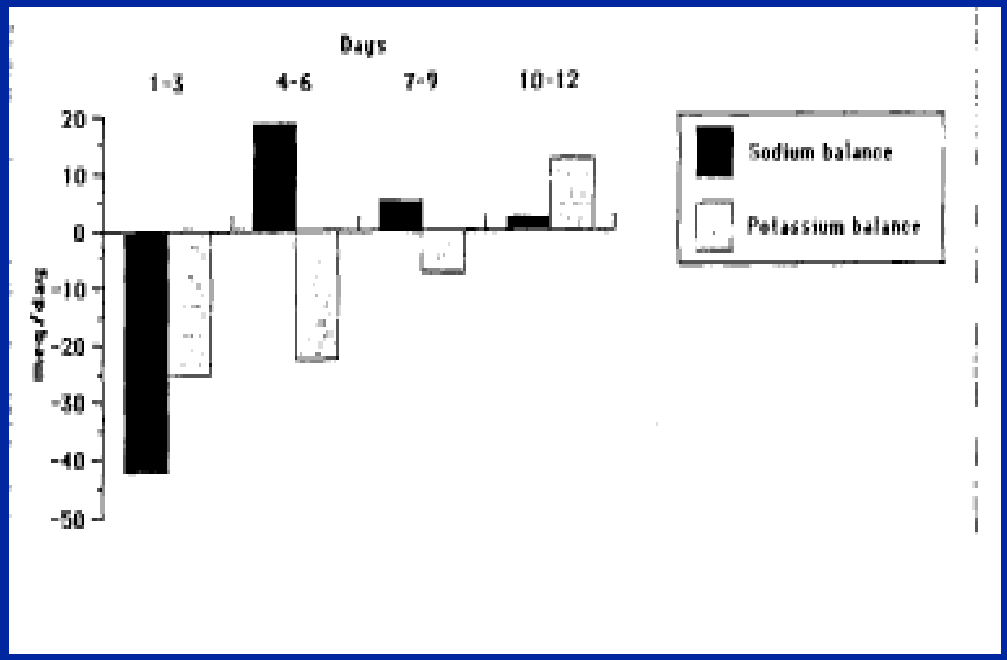
1. More bioavailable drugs (torasemide P.O.).
2. Less hepatic elimination (furosemide iv)
3. Maximizing dose
4. Repeated dosing - constant infusion

# FLUID & ELECTROLYTE COMPLICATIONS OF DIURETIC THERAPY

- VOLUME DEPLETION
- AZOTEMIA
- HYPOKALEMIA
- METABOLIC ALKALOSIS
- HYPERKALEMIA & METABOLIC ACIDOSIS with Potassium sparing drugs (renal failure, ACE inhibitor, $K^+$ supplement)
- HYPONATREMIA (thiazides >> loop agents)
- HYPERURICEMIA
- HYPOMAGNESEMIA
- HYPERCALCEMIA (thiazide in patients with a predisposing condition e.g. sarcoid)

# DIURETICS
## The Steady State

- **Fluid & electrolyte balance are achieved by the maintenance of a steady state.**
- **Perturbations stimulate responses to retain balance.**
- **Time course of diuretic induced metabolic complications [2 -3 weeks] based on responses of compensatory mechanisms.**



# FLUID & ELECTROLYTE COMPLICATIONS OF DIURETIC THERAPY
## Hypokalemia

- **Common problem: Hctz dose of 50mg/d = mean ⇓ $[K^+]$ ▯.▯ meq/L (10% pts will fall to or below 3.0 meq/L.) Long acting chlorthalidone, mean ▯ $[K^+]$ = ▯.▯-▯.▯ meq/L.**
- **Mechanism**
  - **⇑ delivery $Na^+$ and water collecting tubule ( potassium secretory site; aldo sensitive)**
  - **Increased aldosterone secretion due to drug induced decrease in volume**

# FLUID & ELECTROLYTE COMPLICATIONS OF DIURETIC THERAPY

## Hypokalemia

- Less hypokalemia with loop agents
  - ? mechanism: may be due to effect of loop agents on Ca, increased distal delivery may impair sodium handling at distal site and diminish $K^+$ secretion.
- Major concerns: Cardiac arrhythmias (*digitalis),* Increase in BP, Increase incidence of stroke, Can precipitate hepatic coma in advanced cirrhosis, stimulation of renal $NH_3$ synthesis
- Rx: Lower dose of diuretic, $K^+$ supplementation 40-60 meq/d, Use of $K^+$ sparing agents, Correction of magnesium depletion.

# FLUID & ELECTROLYTE COMPLICATIONS OF DIURETIC THERAPY
## Hyponatremia

- Uncommon but potentially fatal
- Thiazides are major cause; rare for loop agents
- Rapid onset: after single dose [$Na^+$] may fall 5-6 meq/L in 6 hours & up to 18 meq/L in 36 hours.
- Mechanism:
  - ADH stimulation by volume depletion or other stimuli (impaired water excretion = water retention)
  - $Na^+$ & $K^+$ excretion induced by diuretic
    ( [combination ] may exceed plasma)

# FLUID & ELECTROLYTE COMPLICATIONS OF DIURETIC THERAPY
## Hyponatremia

- **Mechanism:**
  - **Increased water intake in some patients**
  - **ADH independent water retention**
  - **? decreased intrarenal prostaglandin production ( more common in the elderly)**
- **Prevention: Cannot predict what patient will develop this complication. Caution with elderly patients, use of NSAIDs, monitor closely for first 1-2 weeks.**

# FLUID & ELECTROLYTE COMPLICATIONS OF DIURETIC THERAPY

## Hyperuricemia

- Common; Increased risk in susceptible individuals for gouty arthritis not uric acid nephropathy.
- Diuretics decrease urate excretion
- Urate retention is dose dependent.
- Proximal tubule major site of urate reabsorption & secretion.
- Urate entry is by anion exchange (hydroxyl or lactate). Dependent on $Na^+$ transport.
- Volume depletion = enhanced proximal Na reabsorption.
- Rx: Asymptomatic hyperuricemia need not be treated.

# FLUID & ELECTROLYTE COMPLICATIONS OF DIURETIC THERAPY
## Magnesium

- **Subclinical magnesium depletion appears relatively common after loop/thiazide diuretic exposure. Important to look for associated hypokalemia, particularly unresponsive to K supplementation.**

- **Loop agents decrease electrical gradient ($K^+$ back leak =lumen +) in ascending limb. Decreased passive paracellular $Mg^+$ reabsorption. (Account for 50-60% of filtered Mg reabsorption)**

# FLUID & ELECTROLYTE COMPLICATIONS OF DIURETIC THERAPY

## Magnesium

- Distal magnesium reabsorption takes place in cortical collecting tubule. Cell entry through $Mg^{+}$ channels
- Thiazides increase $Na^{+}$ delivery to cortical collecting tubule & increase $Na^{+}$reabsorption (aldo)
- Postulated that the increase in intracellular [$Na^{+}$] will decrease drive for Na-Mg exchanger (basolateral side).
- Risk: ? increase susceptibility to arrhythmias
- Prevention: Use of $K^{+}$ sparing agents that diminish magnesium excretion.

# FLUID & ELECTROLYTE COMPLICATIONS OF DIURETIC THERAPY
## Calcium

- Loop agents increase calcium excretion.
  - Loop agents decrease electrical gradient ($K^+$ back leak lumen +) in ascending limb. Decreased passive paracellular $Ca^+$ reabsorption.
- Useful for treatment of hypercalcemia.
- Thiazides decrease calcium excretion.
  - Increase proximal $Ca^+$ reabsorption (vol depletion)
  - Increased distal $Ca^+$ reabsorption ( ? mechanism)

# FLUID & ELECTROLYTE COMPLICATIONS OF DIURETIC THERAPY
## Calcium

- **Clinical Effects**
  - **Treatment for idiopathic hypercalciuria with reduction in stone formation.**
  - **Trend to increase Ca balance with reported increases in bone density and decrease in bone fractures. Implications for elderly patients.**
  - **Potential for hypercalcemia in patients, particularly those with underlying disease. i.e.. sarcoid, hyperparthyroidism.**

# DIURETICS
# THERAPY: HYPERTENSION

- Reduction in incidence myocardial infarction
- Reduction in incidence of stroke
- Regression of LVH
- Decrease in incidence of CHF
- Appear to prevent progression from mild to severe hypertension

# THIAZIDE DIURETICS
## THERAPY: HYPERTENSION
## RATIONALE FOR FIRST CHOICE AGENT

- **EFFECTIVE - Long term studies (ALLHAT$_{33,357 subjects}$)**
  - **Lower BP, reduce clinical events**
- **Short dose response curve - 25-50 mg; less titration**
- **Suitable for once per day dosage**
- **Well tolerated**
- **Adverse effects at higher doses only**
- **Potentate actions of newer agents - decrease in BP that is more than additive**
- **Inexpensive**

# DIURETICS
## ANTIHYPERTENSIVE EFFECTS
## Thiazides

- 1st line agents
- Dose 12.5-25 mg alone;  ? 6.25mg with other agents
- Response requires initial volume loss ⇒□□□□ kg (average)
- Fall usually in 1 week may continue for up to 12 weeks.
- Initial response = ⇩□PV, ⇩□CO, ⇧□PRA (AII), ⇧□PVR
- Long term response = ⇧□ PV, ⇧□CO, ⇧□PRA (AII), ⇧PVR
- Mechanism of secondary vasodilatation is unknown.
- Thiazides more effective than loop agents when the GFR is above 20ml/min.

# DIURETIC RESISTANCE CAUSES

- **PATIENT NONCOMPLIANCE**
  - **Not taking drug**
  - **High NaCl intake**
- **IMPAIRED BIOAVAILABILITY**
  - **Congestive heart failure (CHF alters time of absorption rather than % absorbed)**
  - **Idiopathic edema**
- **HEMODYNAMIC ( reduced GFR)**
  - **Drugs: antihypertensives, NSAIDs**
  - **Hypoxemia**
  - **Decreased effective arterial volume**

# DIURETIC RESISTANCE CAUSES

- **IMPAIRED DIURETIC SECRETION by PROXIMAL TUBULE**
  - **Renal failure**
  - **Age**
  - **Congestive heart failure**
  - **Drugs**
  - **Renal transplantation**
- **PROTEIN BINDING IN TUBULE LUMEN**
  - **Nephrotic syndrome**

# DIURETIC RESISTANCE CAUSES

- **ENHANCED NaCl REABSORPTION**
  - **Primary**
    - **Congestive heart failure**
    - **Nephrotic syndrome**
    - **Cirrhosis**
  - **Secondary to drugs**
    - **NSAIDs**
    - **Adaptation to chronic diuretic therapy**

# WHAT DO THESE PATIENTS HAVE IN COMMON ?

- 65 y/o male with congestive heart failure ?
- 54 y/o black woman with end stage renal disease ?
- 30 y/o white man with recurrent calcium oxalate stones ?
- 55 y/o white women with end stage liver disease and ascities ?
- 60 y/o black male on lithium therapy with polyuria ??
- 55 y/o white man about to undergo coronary artery bypass surgery ?
- 10 y/o white girl with proximal renal tubular acidosis ?
- 45 y/o black women with essential hypertension ?
- 50 y/o white women with metastatic breast cancer ?
- 70 y/o black man with CHF and severe metabolic alkalosis ?

# CASES - DIURETICS

- 50 year old black women started on HCTZ eight years ago during prednisone therapy for peripheral edema. Noted to have an elevated uric acid for 5 years and a mild metabolic alkalosis. The prednisone was D/C 5 years ago. Each time the patient attempts to stop the diuretic she experiences mild lower extremity edema and restarts the agent within three days.
- Why does she develop edema ? Why is her uric acid ↑ ?
- Does she need the HCTZ ?
- How would you stop the diuretic?